Extraintestinal manifestations in inflammatory bowel disease - epidemiology, genetics, and pathogenesis

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Abstract: Inflammatory bowel disease (IBD) is a chronic inflammatory disorder, primarily of, but not restricted to the gut. Extraintestinal manifestations (EIMs) are frequently observed and involve the joints, eyes, hepatobiliary tract, and skin. Areas covered: In this review, we discuss classical EIM focusing on epidemiology, genetics, and pathogenesis, highlighting recent advances in the understanding of EIM. We further discuss treatment-induced immunological phenomena, which are increasingly recognized and might challenge IBD-treating physicians in the era of biological treatment. Expert opinion: EIM considerably contributes to morbidity and mortality. Genetic studies have revealed a common genetic background between EIM and IBD and among specific EIM. Identified protein interactions have been shown to cluster in shared biological pathways. However - despite these recent advances - pathogenesis of EIM is at best partially understood. Several pathogenic mechanisms have been proposed such as upregulation of tumor necrosis factor, aberrant lymphocyte homing, and cross-reactive antigen presentation. It still remains unclear whether EIM is a direct result of the inflammatory process in the gut or rather a consequence of a shared genetic background leading to dysfunctional immune responses to environmental stimuli. Exploration and understanding of EIM genetics and pathophysiology will pave the road for better and more efficacious treatment options in the future.

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ABSTRACT (max. 200 words)

INTRODUCTION: Inflammatory bowel disease (IBD) is a chronic inflammatory disorder, primarily of, but not restricted to the gut. Extraintestinal manifestations (EIM) are frequently observed and involve the joints, eyes, hepatobiliary tract and skin.

AREAS COVERED: In this review, we discuss classical EIM focusing on epidemiology, genetics and pathogenesis, highlighting recent advances in the understanding of EIM. We further discuss treatment-induced immunological phenomena, which are increasingly recognized and might challenge IBD-treating physicians in the era of biological treatment.

EXPERT COMMENTARY:

EIM considerably contribute to morbidity and mortality. Genetic studies have revealed a common genetic background between EIM and IBD, and among specific EIM. Identified protein interactions have been shown to cluster in shared biological pathways. However – despite these recent advances – pathogenesis of EIM is at best partially understood. Several pathogenic mechanisms have been proposed such as upregulation of TNF, aberrant lymphocyte homing and cross-reactive antigen presentation. It still remains unclear whether EIM are a direct result of the inflammatory process in the gut or rather a consequence of a shared genetic background leading to dysfunctional immune responses to environmental stimuli. Exploration and understanding of EIM genetics, pathophysiology will pave the road for better and more efficacious treatment options in the future.

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1. INTRODUCTION

Inflammatory bowel disease (IBD) with its two subtypes Crohn`s disease (CD) and ulcerative colitis (UC), is defined as a chronic inflammation of the intestine, which arises from a complex interplay between a dysfunctional host immune response and environmental triggers.[1,2] However, it has become apparent that IBD is a systemic disorder, that primarily affects the gut, but which is not restricted to the intestinal tract. So-called extraintestinal manifestations (EIM) – an umbrella term for IBD-associated manifestations outside of the gut – are indeed frequently observed.[3,4] EIM considerably contribute to morbidity and mortality in IBD patients.[5,6] Yet, there is no uniform definition of EIM. Published reviews and studies included different sets of EIM. In most analyses, EIM are at least distinguished from IBD-associated complications such as osteoporosis, anemia or micronutrient deficiency. These complications are a direct consequence of the intestinal inflammation rather than a distinct inflammatory process. EIM can be defined as an inflammatory entity caused by the same processes that drive inflammation in the gut, but which is located outside of the intestine, in a patient with IBD.[2] From a more mechanistic perspective, EIM may be classified into *specific*, *reactive*, *associated* and *treatment-induced*.[4,7] While *specific* EIM represent the same disease as IBD, but are located outside of the gut (such as metastatic or mucocutaneous CD), *reactive* EIM share pathogenic mechanisms with IBD without exhibiting the same histomorphological characteristics.[4] For *associated* EIM, pathogenic link remains unclear, but they are more frequently observed in the context of IBD compared to controls. Treatment-induced EIM show a temporal association with IBD treatment and disappear upon cessation of the culprit treatment regimen.[8] Due to the rarity of some EIM, determination of their association with IBD is challenging and might be confounded by a recall bias resulting in an overestimation of the association between EIM and IBD. Furthermore, it still remains unclear whether EIM are a direct result of the inflammatory process in the gut or rather a consequence of a shared genetic background leading to dysfunctional immune responses to environmental stimuli. In this review, we will discuss classical EIM focusing on epidemiology, genetics and pathogenesis, particularly highlighting advances in understanding of EIM in recent years. Finally, we will discuss treatment-induced immunological phenomena, which are increasingly recognized and might challenge IBD-treating physicians in the era of biological treatment.

2. CLASSIFICATION OF EIM

A classical definition of EIM includes the four following organ systems: 1) musculoskeletal system (arthritis, spondylarthropathy); 2) eyes (episcleritis, uveitis), 3) skin (pyoderma gangrenosum, erythema nodosum, stomatitis); and 4) hepatobiliary system (primary sclerosing cholangitis (PSC)).[2,3] These EIM may or may not parallel intestinal disease activity; Erythema nodosum, episcleritis and type 1 arthritis are typically associated with intestinal disease, while spondylarthropathy and type 2 arthritis do not correlate with intestinal inflammation. For some EIM such as pyoderma gangrenosum or uveitis correlation with intestinal disease activity is less clear.[9-12] For details see **Figure 1**. Recent studies revealed that EIM mostly manifest after the diagnosis of IBD is established, within a median of 92 months. However, in a non-negligible proportion of patients (25.8%) EIM occur before IBD. In these patients median time from EIM to IBD is 5 months, although in some patients EIM might be found more than two years before IBD diagnosis.[13] Similar findings are reported in the pediatric IBD population.[14] In the following, we will describe classical EIM and their clinical presentation in more detail.

Musculoskeletal

Musculoskeletal EIM include three disease entities: 1) type 1 peripheral arthritis, 2) type 2 peripheral arthritis, and 3) axial spondylarthropathy. Peripheral arthritis shows a non-destructive course.[2,8] It usually is seronegative; neither rheumatic factor nor anti-nuclear antibodies can be detected.[9] Peripheral arthritis is more frequently observed with colonic and/or perianal involvement and is further associated with erythema nodosum, stomatitis and pyoderma gangrenosum.[9,15] The following classification can be applied: type 1 vs. type 2. Type 1 is a pauciarticular manifestation with involvement of less than 5, mostly large joints such as knee or ankle. Disease course is acute, often asymmetrical and migratory.[2] It usually parallels intestinal disease activity.[16] In contrast, type 2 arthritis affects smaller joints (most often MCP), shows involvement of 5 or more joints and runs independently of intestinal disease activity.[2] While type 1 arthritis is usually self-limiting, type 2 disease can persist up to several years.[16] Given the absence of serum markers and missing destruction on plain films, diagnosis is typically made based on clinical examination.[17] Arthritis should be distinguished from arthralgia, which is simple joint pain without any evidence of inflammation.[8] The latter is frequently observed and non-specific. Axial spondylarthropathy affects the spine and/or the sacroileal joint. It can be subclassified into ankylosing spondylitis

and sacroiliitis.[2] Ankylosing spondylitis presents similarly to the non-IBD associated form: Patients, particularly males, complain of worsening back pain, which starts at relatively young age. Further symptoms are morning stiffness and aggravating pain during rest. On clinical examination, spine mobility is considerably decreased. In early stages, plain films might be normal, while in later stages, typical findings such as syndesmophytes, vertebral body squaring and ankylosis can be detected.[2] In contrast to ankylosing spondylitis, isolated sacroiliitis is more frequently seen.[18-21] It ususally does not show progression to ankylosing spondylitis. However, this risk is increased with bilateral joint involvement.[22] The diagnosis of spondylarthropathies can be made based on symptoms, clinical examination and radiographic findings.[8] MRI is more sensitive than plain films, particularly in early disease stages.[23,24] Given an association with HLA-B27 (see genetics),[25] testing for this HLA genotype might be helpful in case of diagnostic uncertainties.

Skin

Skin manifestations of IBD have been described in more detail very lately.[4] Briefly, the typical cutaneous EIM include erythema nodosum, pyoderma gangrenosum, and stomatitis.[4,8] The latter has to be distinguished from CD of the oral cavity. Erythema nodosum is clinically defined as symmetric, raised, tender, red-violet subcutaneous nodules.[2] Their diameter vary from 1 to 5cm. Erythema nodosum typically localizes on the extensor surfaces of the lower extremities, the anterior tibia is its most frequent localization.[26] While erythema nodosum is known to parallel intestinal disease activity, severity does not correlate with degree of intestinal inflammation.[27,28] Risk factors are colonic involvement and occurrence of other EIM, particularly pyoderma gangrenosum.[29] Pyoderma gangrenosum is the most severe and debilitating cutaneous manifestation in IBD.[4] It is characterized by a fast development from a painful erythematous papule or pustule to a dermal necrosis and finally deep ulcerations with purulent, but sterile discharge.[8] Pyoderma gangrenosum commonly localizes on the shin or in the peristomal area.[2] It might be accompanied by systemic symptoms. Diagnosis can be made based on clinical examination. Biopsies might be helpful to rule out infection, but any manipulation may worsen the disease.[30] This phenomenon is known as pathergy effect.[31] Mucocutaneous EIM in the oral cavity include (aphthous) stomatitis and periodontitis. Typical findings are painful ulcers of the labial and buccal mucosa.[30] Peristomatitis vegetans is its most severe form.[4,30] Periodontitis presents as gingival swelling and redness.[32] These oral manifestations usually parallel intestinal inflammation.

Ocular

Episcleritis and uveitis are the most common ocular manifestations in IBD.[8] While episcleritis describes a mild disease, uveitis is usually more severe and may result in visual impairment. Episcleritis is defined as an inflammation of the episclera, which presents with a painless injection of the sclera and conjunctiva.[2,33] Burning and itching may be present. In contrast, uveitis manifests with considerable pain, photophobia, blurred and eventually decreased vision. Uveitis can be categorized into the following four subtypes depending on the localization of inflammation: 1) anterior (=iritis), 2) intermediate (=vitritis), 3) posterior (=choroiditis), and 4) panuveitis.[8] While episcleritis paralles intestinal disease, uveitis does not.[34] Urgent ophthalmologic examination (with a slit-lamp) is warranted in case uveitis is suspected.[8,33]

Hepatobiliary

PSC is a cholestatic liver disease, characterized by inflammation and fibrosis of the biliary tract.[35] It considerably contributes to morbidity and mortality, particularly in UC patients.[8,36] Cancer risk – both for colorectal cancer and cholangiocellular carcinoma – is increased.[37-40] Risk factors for PSC are: 1) extensive colitis, 2) backwash ileitis, and 3) male sex.[11,41] PSC is diagnosed based on a cholestatic pattern of liver enzymes and biliary strictures, segmental dilations on MRCP or ERCP.[8,42-44] Other hepatobiliary manifestations of IBD include fatty liver, granulomatous hepatitis, autoimmune liver disease, and pancreatitis.[45]

3. EPIDEMIOLOGY

Overall, 6-47% of IBD patients experience at least one EIM.[18,26,46-51] Arthritis is the most common EIM, followed by stomatitis, uveitis, erythema nodosum and axial spondylarthropathy.[3] In a considerable proportion of patients (36.6%), more than one EIM are observed. A subset of patients (2.7%) may actually present with up to five EIM. Several factors increase the likelihood of developing EIM: 1) EIM are significantly more frequent in CD compared to UC patients;[3,14,52] 2) EIM are more frequent with longer IBD duration;[51] 3) In CD patients, female sex, age, and disease activity have been identified as independent predictors for the presence of EIM;[3] and 4) In UC, extensive colitis was significantly associated with the presence of EIM.[6] EIM typically manifest after the diagnosis of IBD has been established with a median time from IBD to first EIM of more than 7 years.[13] Nonetheless – at least in a subset of patients (25.8%) – EIM can also occur before IBD

diagnosis. This was particularly seen for uveitis (52.2%) and axial spondylarthropathy (39.1%).[13] Other EIM such as pyoderma gangrenosum and erythema nodosum rarely manifest before IBD diagnosis. In contrast to the increasing knowledge about EIM in adult IBD, much less is known about EIM in the pediatric population. At IBD onset, EIM appear to be more frequent in children compared to adults.[14,53] However, frequency overall seems to be lower than in the adult population, which might be attributed to a shorter IBD duration.[14,54,55] Otherwise, EIM appear to be fairly similar in children and adult: Our group has recently shown that EIM are more frequent in CD than UC, and that the most frequent EIM is arthritis followed by aphthous stomatitis and uveitis.[14] There are only minor differences such as higher rates of arthritis and lower rates of spondylarthropathies in children compared to adults.[14] In the following, we discuss the epidemiology of specific EIM in more detail focusing on data from adult cohorts. In general, prevalence of EIM has been reported with a large variation. This might be attributed to different definitions of EIM, different study designs (prospective vs. retrospective) and considerable differences regarding EIM diagnostics.

Musculoskeletal

Peripheral arthritis has been reported with a prevalence ranging from 5 to 20%. It appears to be more common in CD (10-20%) than UC (5-10%) and is more frequently observed in females.[8,16] Colonic involvement has been identified as a risk factor for the presence of peripheral arthritis.[2,9] Spondylarthropathies occur in up to 25%, but most studies reported lower frequencies.[6,26,49-51] Subclinical disease – diagnosed based on radiographic findings – appears to be more frequent.[2,18] Males are more commonly affected.[2]

Skin

In contrast to most EIM, pyoderma gangrenosum is more common in UC than CD.[56-59] Females are more often affected.[60] The prevalence of pyoderma gangrenosum is however rather low; it ranges from 0.4 to 2%.[3,18,58,59] Erythema nodosum is more frequently seen than PG, its prevalence has been reported with up to 15%.[2,26] It is considered the most frequent cutaneous manifestation of IBD.[4] Frequency appears to be higher in CD than UC, and also in females compared to males. Stomatitis is also a common cutaneous IBD manifestation.[3,50] In the Swiss IBD cohort, its prevalence was 7.4% (CD 9.8 vs UC 3.5%).[3] Exact numbers for peristomatitis vegetans, a particularly severe form of stomatitis, are currently unknown. Prevalence of periodontitis in IBD has not been systematically assessed. However, a case-

control study showed its association with IBD, particularly perianal disease.[32] Periodontitis per se, regardless of IBD, is however relatively common (up to 50%).[61]

Ocular

4-12% of IBD patients have ocular manifestations.[62] Ocular EIM are more frequent in CD than UC.[3,6,26,49,51] In some cohorts, prevalence is reported with up to 29%.[8,62] Most patients present with episcleritis, while uveitis is less common with a prevalence of 0.5-3%.[12] The Swiss IBD cohort – however – reported higher uveitis rates (5.3%).[3] Very severe forms, such as scleritis, intermediate or posterior uveitis are extremely rare.[63]

Hepatobiliary

PSC is the most common IBD-specific hepatobiliary manifestation.[44] Prevalence has been reported with 4-5%.[64,65] However, geographic variation in PSC prevalence has been observed.[66] In the nation-wide Swiss IBD cohort, PSC was detected in 1.8% of all patients, and in 3.5% of patients with UC, which are at increased risk for disease development. In contrast to PSC, non-specific hepatobiliary manifestations are more frequently encountered: It is estimated that up to 30% of IBD patients present with abnormal liver function tests or are affected by hepatobiliary manifestations during the course of their disease.[67]

4. GENETICS

EIM are frequently associated with each other, and the presence of one EIM increases the risk for further EIM.[3,13,68] More than a third of patients presents with at least two EIM, while 10% report three or more EIM.[13] One explanation for these findings are that EIM share common genetic pathways. NOD2, which is a well-known risk factor for CD, has been identified as risk factor for sacroileitis and uveitis, two common EIM in CD.[69,70] Based on association studies, epidemiological data and genome-wide association studies, it has become increasingly apparent that genetics contribute to the development of EIM. An extensive summary of possible genetic factors has been recently published in an ECCO workshop paper.[71]

Epidemiological studies

The impact of genetic factors on the development of EIM has first been suggested by findings from association studies showing concordance of EIM in 70% of parent-child pairs and 84% of sibling pairs.[72] Furthermore, high rates of positive family history of IBD were observed in patients presenting with EIM. Indeed, positive family history is an independent

predictive factor for the occurrence of EIM in CD patients.[3] Population-based studies further revealed different prevalence rates for EIM in the West (17-63%) compared to the East (5-40%).[66,73] Such difference is particularly seen for PSC, which is less frequently reported in Asia than in the Western hemisphere.[66] The likelihood of diagnosing an underlying IBD associated with PSC, is considerably lower in the East compared to the West.[74-78] Besides geographic differences in EIM and PSC prevalence, frequency of EIM appears to be different among specific ethnic groups: Joint complications are more frequently seen in African-Americans and Asians, while EIM per se appear to be more common among Indians compared to Malays and Chinese.[79,80] These data indicate: 1) a possible common genetic background in EIM patients; and 2) a contribution of genetic factors to the development of EIM.

HLA genotypes

Human leukocyte antigens are recognition molecules that initiate immune responses. Polymorphism in HLA genotype can increase the susceptibility for the development of auto-inflammation.[81] Indeed, genetic variations in HLA have been shown to increase the risk for specific EIM. One of the best-known genetic risk factors for occurrence of EIM is HLA-B27. HLA-B27 has been associated with joint, skin and ophthalmologic manifestations, particularly axial spondylarthropathy and type 1 arthritis. This association is rather specific: Patients with axial spondylitis are positive for HLA-B27 in 50-90%, while for patients with sacroiliitis without spondylarthropathy HLA-B27 positivity is only seen in 7-15%.[8,82] However – despite this association with EIM – HLA-B27 does not increase the risk for IBD.[46] Further identified HLA genotypes associated with EIM are: 1) HLA-B8/DR3 for PSC, 2) HLA-B35 for type 1 arthritis, 3) HLA-B44 for type 2 arthritis, 4) HLA-B58 for skin, joint and ophthalmologic manifestations, and 5) HLA-DRB1*0103 for skin, joint and ophthalmologic manifestations, particularly type 1 arthritis.[12,83-85] Several HLA increase the risk of EIM per se, irrespective of a specific EIM subtype: Increased risk of EIM has been observed among CD patients with HLA-A2, HLA-DR1 and HLA-DQw5, while in UC such increase was associated with HLA-DR103, HLA-B58, and HLA-B27.[12,84,86] Taken together, many EIM seem to share a common genetic background in terms of HLA genotypes, although at least some EIM represent immunogenetically distinct entities (such as type 1 vs. type 2 arthritis). It has yet to be determined if HLA polymorphisms indeed increase EIM rates in IBD or rather predispose to IBD subtypes, which are associated with higher EIM frequency.

Genome-wide association studies

Genome-wide association studies (GWAS) are a powerful tool to investigate similarities between diseases in terms of a shared genetic background. Several known IBD risk loci have been linked to EIM highlighting a considerable genetic overlap.[87-92] However, at least for PSC, no such overlap was seen indicating a rather immunogenetically distinct background.[8,93] IBD risk loci, which are associated with EIM, are shown in **Table 1.**

Implications of genetic studies in EIM and IBD

Protein interactions identified by genetic studies may cluster in shared biological pathways.[87] So, genetic studies can help to elucidate EIM pathogenesis and to identify novel mechanisms such as the druggable JAK-STAT pathway. Investigating the function of newly discovered genes involved in EIM pathogenesis may help to unravel novel therapeutic targets. However, such analyses do not answer the question, whether EIM are a true consequence of IBD, or if EIM and IBD are different manifestations of a genetically determined, dysfunctional host immune response to environmental stimuli.

5. PATHOGENESIS

The pathogenesis of EIM is at best partially understood. A common pathogenic pathway is suspected since one EIM increases the susceptibility for another EIM and because EIM tend to appear simultaneously.[13] From a high level perspective, EIM may arise from expansion of intestinal disease activity beyond the gut mediated through various mechanisms such as aberrant lymphocyte homing or cross-reactivity. EIM may also simply develop from a proinflammatory state with upregulation of specific cyto- and chemokines resulting in a dysbalance of immunocomponents. Most probably, several specific pathomechanisms are involved, which are not mutually exclusive. In the following, we discuss pathogenic factors, which have been proposed to contribute to the development and presence of EIM, in more detail. For an overview see **Table 2**.

TNF-pathway

In IBD, antigen-presentation to antigen-presenting cells (APC) and the interaction of APC with T helper cells lead to activation of macrophages. Activated macrophages then produce a mix of broadly active inflammatory cytokines, including tumor necrosis factor (TNF).[94] TNF exhibits its action through binding to death receptors of the TNF receptor family.[95] These receptors can trigger caspase activity and apoptosis in response to ligand binding.[96] TNF can

also further enhance inflammatory response through the NFkB pathway, which leads to upregulation of various interleukins, cyto- and chemokines.[94] Inhibition of TNF signaling has been a successful strategy in IBD treatment. It has further been a strategy in other chronic inflammatory diseases such as psoriasis and rheumatoid arthritis. Recent studies have suggested efficacy of anti-TNF in the management of various EIM.[97,98] Anti-TNF appear to be particularly efficacious in the treatment of cutaneous EIM and arthritis, although most data evolve from non-controlled open-label trials or non-interventional (retrospective) studies. Best evidence is available for pyoderma gangrenosum, where a randomized-controlled trial revealed response rates of 46% and complete remission of 21%.[99] These data have indicated a common TNF-shared pathogenic link between IBD and EIM, and among specific EIM. Our group has identified upregulation of the TNF-NFkB pathway in human biopsy specimens from erythema nodosum and pyoderma gangrenosum.[100] Interestingly, this upregulation was higher than that seen for psoriasis. However, despite this growing evidence for TNF involvement in the pathogenesis of EIM, it remains unclear if this represents an expansion of intestinal disease activity to extraintestinal sites or if it is rather the consequence of a generally pro-inflammatory state (dysbalance of cytokines) in genetically susceptible patients. The latter might be supported by the fact that TNF is not only increased in intestinal lesions, but also detected in the serum of IBD patients.

Cross-reactive antigens and gut-synovial axis

Cross-reactivity of antigens (molecular mimicry) is a known mechanism of autoimmune diseases. When foreign antigens share sequences or structural similarities with self-antigens, autoimmune response can be triggered.[101] In the context of IBD and EIM, microbiota antigens are of particular importance. It has been shown that germ free HLA-B27 transgenic mice are not able to develop joint inflammation.[102] This indicates that exposure to bacterial antigen is a sine-qua-non for the development of spondylarthropathy, even in the context of a genetic predisposition.[103] This importance of bacterial exposure in the gut in the pathogenesis of EIM is referred to as the so-called gut-synovia axis. Th1/Th17 lymphocytes are primed in the gut, which then home to synovial tissue triggering an inflammatory response.[104] It has yet to be determined if microbiota can be effectively targeted to treat EIM.

Aberrant lymphocyte recruitment/homing

Gut-specific lymphocytes might invade extraintestinal sites if they express gut-specific chemokine or integrin receptors.[105,106] This has been shown for PSC, in particular.[106] However, beyond PSC, there is not much evidence for such ectopic expression of receptors leading to aberrant lymphocyte homing. Our group has recently analyzed 31 biopsy samples from erythema nodosum and pyoderma gangrenosum showing no evidence for expression of gut-specific MAdCAM in the skin.[100] However, lymphocytes might co-express gut-specific and skin-specific homing ligands, which enable tropism to extraintestinal sites.[107] Other mechanisms are the use of non-specific ligands and receptors for lymphocyte-endothelial cell interaction such as VAP-1, which is expressed in the gut, eyes and joints.[107,108] Despite absence of MAdCAM expression in non-intestinal tissue, recent studies suggested efficacy of vedolizumab in EIM management; complete remission of inflammatory arthralgia/arthritis and cutaneous EIM was achieved in 44.7 and 75%, respectively.[109] Improvement was mainly associated with quiescent IBD. Thus, it remains elusive whether this is a direct effect of vedolizumab on EIM or whether this rather happens indirectly through controlling intestinal disease activity.

Taken together, both specific and non-specific lymphocyte-endothelial cell interaction may induce lymphocyte homing to different organs and promote inflammation at extraintestinal sites.

Autoimmune mechanism

Autoimmune mechanisms appear to be involved at least in some EIM. Circulating perinuclear anti-neutrophil cytoplasmic antibodies (p-ANCA), which can be found in serum from CD patients, have been linked to PSC, EN and uveitis.[83] In addition, vasculitis with deposition of complement factor C3 in the endothelial basement membrane is a frequent finding in biopsies from patients with aphthous stomatitis.[110] However, it has yet to be determined if these antibodies are pathologically relevant or rather an epiphenomenon.

Environmental factors

Although auto-inflammatory processes arise from an exposure to environmental triggers in genetically susceptible patients, not much is known about external factors in the pathogenesis of EIM. Relative rarity of events is the main limitation to identify pathogenic environmental factors. In addition, results may be confounded by a recall bias. Nonetheless, in a cross-sectional analysis of three IBD cohort studies, smoking has been identified as an independent risk factor for EIM in both CD and UC.[111] Of note, this association between

smoking and EIM was dose-dependent.[111] Furthermore, smoking cessation was associated with a reduction of EIM prevalence.[111] Both findings make the results more reliable. Yet, prospective trials are missing showing positive effects of smoking cessation on specific EIM. Nonetheless, based on the current data, smoking cessation should be recommended in all patients.

Other proposed mechanisms

Other pathogenic mechanisms have been proposed, particularly for cutaneous manifestations,s such as abnormal neutrophil function and impaired cellular immunity in pyoderma gangrenosum, type III hypersensitivity reaction in Sweet`s syndrome, which is a systemic form of neutrophil dermatosis, and type IV hypersensitivity in erythema nodosum.[8,30,112,113]

6. TREATMENT INDUCED IMMUNOLOGICAL LESIONS

Treatment-induced inflammatory manifestations have long been an under-reported problem, but they have received growing attention in recent years.[114,115] With the wide use of biologics, anti-TNF in particular, reports on such manifestations have been rapidly increasing. While in 2009, a total of only 127 patients presenting with anti-TNF induced manifestations have been reported, the prevalence is nowadays considered to be up to 22% in some cohorts.[8,116] The inclusion of treatment-induced lesions as EIM is controversial; some reviews rather consider them as treatment-induced side effects. However, given their likely immunological background and since the first ECCO guidelines on EIM clearly consider them amongst EIM, we herein discuss treatment-induced inflammatory manifestations in more detail. Diagnosis of treatment-induced lesions is usually clinical-based and includes: 1) assessment of time-point of appearance (after initiation of treatment); 2) disease course after discontinuation of treatment (they usually disappear and resolve completely); and 3) possible re-challenge with the same agent. The most frequent treatment-induced inflammatory manifestations are discussed in the following section with a focus on anti-TNF and vedolizumab.

Anti-TNF

Anti-TNF induced skin lesions are the best-studied treatment-induced manifestation in IBD. These lesions present as either eczematiform or psoriasiform skin eruptions.[4] Eczematiform eruptions are characterized by xerosis and pruriginous plaques with erythematous or

squamous vesicles, while a psoriasiform presentation exhibits scaly erythematous plaques, pustulosis and eventually nail involvement.[8,117] The frequency of anti-TNF induced skin lesions is reported with 5-10%, but higher rates were detected in some cohorts.[8,115,118] These lesions usually respond well to local treatment (eg steroids) and anti-TNF agents can often be continued.[4] However, in up to 34% cessation of treatment is necessary.[118] A switch to another anti-TNF agent is not recommended given a class-effect. Ustekinumab, an IL12/23 antibody, has been successfully used as an alternative treatment option.[119] Anti-TNF induced joint manifestations – inflammatory arthralgia or arthritis – are considerably less frequent than skin lesions.[115,120] These manifestations are frequently associated with positive anti-nuclear antibodies (ANA) and anti-ds DNA antibodies.[121] Only few cases of ocular manifestations (uveitis, scleritis) have been described.[122,123] A special anti-TNF induced manifestation is the lupus-like syndrome, which presents with fever, rash and arthralgia.[115] ANA and anti-dsDNA antibodies can be detected. Withdrawal of the offending drug results in complete resolution of the syndrome. However, symptoms might recur with a second anti-TNF. Switch to certolizumab might be favorable given lower frequency of ANA positivity.[115] In contrast to the rarity of lupus-like syndrome, ANA and anti-ds DNA antibodies can be found in up to 46-57% of asymptomatic, anti-TNF treated patients.[124] The pathogenesis of anti-TNF induced inflammatory manifestations remains incompletely understood. Different mechanisms have been proposed: 1) increased IFNalpha production, 2) cytokine imbalance, 3) compensatory T-cell expansion, and 4) autoimmunity.[4] [115] TNF is known to inhibit maturation of plasmocytoid dendritic cells (PDC) from hematopoietic progenitor cells.[125] PDC can produce IFNalpha, an important mediator in psoriasis. Anti-TNF agents can therefore de-inhibit this maturation, which leads to an increase of PDCs and finally IFNalpha production.[126] Anti-TNF treatment might also result in a compensatory expansion of Th1/Th17 cells in areas other than the gut, which triggers inflammation in extraintestinal sites such as the skin.[127,128] Anti-TNF mediated reduction in clearance of immunocomponents can further lead to a cytokine dysbalance, while increased exposure of cellular nuclear components may result in antibody formation (such as ANA and anti-dsDNA in lupus-like syndrome). [114,115]

Vedolizumab

Extraintestinal effects of vedolizumab, an anti-integrin a4b7 antibody, has been questioned given the gut-specific expression of MAdCAM1, which acts as receptor for a4b7.[100] However,

as previously stated, there is growing evidence that vedolizumab can positively affect EIM disease course. A comprehensive analysis of 294 vedolizumab-treated IBD patients revealed complete resolution of joint manifestations in 44.7%, which was particularly attributed to clinical remission of IBD.[109] In a case series, vedolizumab had positive effects on pyoderma gangrenosum, uveitis, erythema nodosum, arthropathy and spondylarthropathy.[129] However, compared to anti-TNF, prevention of EIM appears to be less effective, most probably due to a more gut-specific mode of action.[130] Nonetheless, despite positive effects, vedolizumab has also been associated with treatment-induced inflammatory manifestations such as arthralgia/arthritis (13.8%) and skin-lesions (4.8%).[109] Pathomechanisms of these paradoxical manifestations remain unclear. They might be a consequence of aberrant lymphocyte homing or compensatory T cell expansion at extraintestinal sites.

Others

Not much is known about the potential of other biologics to cause treatment-induced inflammatory manifestations. Ustekinumab has been associated with development of pustular psoriatic skin lesions despite its positive effect on anti-TNF induced skin manifestations. Nothing is known with regards to JAK inhibitors, but non-specific rash has been described as possible side-effect.[131]

7. CONCLUSIONS

Extraintestinal manifestations in IBD are frequent and considerably affect morbidity and mortality. A strong genetic background is increasingly recognized. Pathogenesis – however – remains at least partially elusive, and most probably several not mutually exclusive mechanisms are involved such as molecular mimicry, aberrant lymphocyte homing and cytokine imbalance with upregulation of proinflammatory cytokines such as TNF. Treatment-induced immunological phenomena are observed with an increasing frequency. As we learn, these treatment-induced manifestations are not restricted to anti-TNF therapy. Elucidation of genetic and pathogenic mechanisms of both EIM and treatment-induced manifestations will eventually help to identify novel therapeutic targets in the future.

EXPERT COMMENTARY

Extraintestinal manifestations of CD and UC represent a challenge in clinical IBD practice. Extraintestinal does not only indicate *outside of gut*, it also means *outside of the scope* of many gastroenterologists. However, consideration and diagnosis of EIM is key for various reasons: 1) EIM considerably affect morbidity and mortality; 2) EIM can indicate ongoing intestinal disease activity despite absence of symptoms; and 3) EIM can present before a diagnosis of EIM is established. Therefore, presence of EIM should prompt physicians to screen for IBD in non-IBD patients and to assess intestinal disease activity in IBD patients. Although there has long been a consensus that IBD is not restricted to the intestinal tract and rather represents a systemic inflammatory disease, it took a long time until the first guidelines on EIM have been published. This might be attributable to the fact that EIM fall into a nebulous space between gastroenterology and non-gastroenterology subspecialities such as rheumatology, ophthalmology and dermatology. It has now become apparent that – in order to provide the best care for IBD patients – a multidisciplinary approach is needed. Such close interaction and collaboration between specialists will be key to success for both clinical care and research. In the era of biological treatment, the gastroenterologist is more than ever rather a team player than an individualist.

Clinical, translational and basic research are currently limited by the lack of a clear, uniform and generally accepted definition of EIM. Particularly the inclusion of both non-inflammatory arthralgia and inflammatory arthropathy result in inaccuracy and make it more difficult to draw clear conclusions from some observational studies. Further limiting factors are the relative rarity of some EIM, which results in low number of patients in cross-sectional analyses, and the retrospective study design of most published analyses. However, the release of the first ECCO consensus guidelines certainly boosted the field and and several important advances have been achieved in recent years. It has become apparently clear that EIM have a strong genetic background and specific pathomechanisms have been identified contributing to EIM development. Further mechanistic studies will help to unravel EIM pathogenesis, which will ultimately lead to the identification of novel therapeutic targets. Findings from genetic studies facilitate the identification of such novel, potentially druggable pathways. From our perspective, the following research tasks are key and will be likely addressed in the near future:

- Finding consensus regarding a uniform and widely accepted definition of EIM

- Exploration of EIM pathogenesis
- Investigation of frequency and pathogenesis of non-anti-TNF mediated treatment-induced manifestations

Ultimately, one of the burning questions in EIM research is: *Are EIM a direct consequence of the intestinal disease? Or are IBD and EIM two manifestations of a genetic susceptibility with an abnormal immune response to external stimuli?*

Addressing these tasks and questions may pave the road for better and more efficacious treatment options in the future.

FIVE-YEAR VIEW

Given the relative rarity of some EIM, particularly in a cross-sectional setting, multicenter approaches to increase case load and access to patient samples will be key for successful EIM research in the future. Single cell RNAseq analyses are a novel and interesting tool to study EIM pathogenesis. Single cell sequencing can characterize cell subpopulations in more detail than the traditional FACS analyses. Applying this technique to T cells from intestinal and extraintestinal sites will eventually address the question whether or not inflammation at extraintestinal sites represents the same disease as seen in the intestine. Decreasing costs and better accessibility will facilitate its use in the future. Introduction and increasing use of novel biological agents such as JAK inhibitors, anti-integrins and anti-IL12/23 will likely show if treatment-induced lesions are unique to anti-TNF or if they can occur with any drug interfering with IBD pathogenesis.

KEY ISSUES

- EIM are frequent and considerably affect morbidity and mortality in IBD patients.
- EIM have a strong genetic background.
- Pathogenesis of EIM is at best partially understood. Several not mutually exclusive mechanisms are involved, such as cross-reactivity, cytokine imbalance and aberrant lymphocyte homing.

DISCLOSURES

T. Greuter has declared associations with Sanofi, Falk, Vifor and Novartis. S.R. Vavricka has declared associations with Abbott, Fering, MSD, Pfizer, Takeda, Tillots, UCB, Vifor and Falk. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

LEGENDS

Figure 1: Classification of EIM and association of specific EIM with IBD. Green dots indicate association with intestinal disease activity, while red dots indicate that EIM do not parallel intestinal disease activity. Green and red dots together indicate that this specific EIM may or may not parallel intestinal disease activity.

Table 1: Genetic risk factors for development of extraintestinal manifestations.

Table 2: Proposed pathogenic mechanisms for extraintestinal manifestations.

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TABLES

Table 1

Analyses	Genetic risk factors
HLA genotypes	HLA-B27: joint, skin and opthalmologic manifestations, particularly axial spondylarthropathy HLA-B8/DR3: PSC HLA-B35: type 1 arthritis HLA-B44: type 2 arthritis HLA-B58: joint, skin and opthalmologic manifestations HLA-DRB1*0103: joint, skin and opthalmologic manifestations HLA-A2: EIM in general HLA-DR1: EIM in general HLA-DQw5: EIM in general
GWAS for axial spondylarthropathy and IBD	IL23R IL12B STAT3 PTERG4 CARD9 IL1R2 ORMDL3
GWAS for psoriasis and IBD	IL12B IL23R JAK2 STAT3
GWAS for EN and IBD	CLCA2 LY75 2q24.1
NOD2	Risk factor for ileal CD, sacroileitis, and uveitis

Table 1: Genetic risk factors for development of extraintestinal manifestations. EIM, extraintestinal manifestatinos; EN, erythema nodosum; GWAS, genome wide association study; HLA, human leukocyte antigen; IBD, inflammatory bowel disease

Table 2

Pathogenic mechanisms	
TNF pathway	Upregulation of TNF at extraintestinal sites in the context of EIM such as EN or PG.
Cross-reactivity	Microbiota antigens sharing similarities with self-antigens, gut-synovia axis
Autoimmunity	Circulating antibodies (p-ANCA), vasculitis with C3 deposition
Aberrant lymphocyte homing	Lymphocyte homing to extraintestinal sites due to ectopic expression of gut-specific receptors (MAdCAM1), co-expression of gut- and extraintestinal-site-specific ligands (a4b7 integrin and CLA), and expression of non-site-specific ligands (VAP-1)
Others	Abnormal neutrophil function, impaired cellular immunity, Type III hypersensitivity reaction, Type IV hypersensitivity

Table 2: Proposed pathogenic mechanisms for extraintestinal manifestations. EN, erythema nodosum; IBD, inflammatory bowel disease; PG, pyoderma gangrenosum; TNF, tumor necrosis factor